

### REMARKS

Claims 57-73 and 82-144 constitute the pending claims in the present application. Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

Applicants note that the RCE filed October 29, 2002, has been entered and considered.

### *Specification*

The specification remains objected to under 35 U.S.C. § 132 as allegedly containing new matter. For the reasons already of record, Applicants submit that this objection is without legal merit, because the added portions were properly incorporated by reference. Nevertheless, to create a clear record for the purposes of appeal, Applicants reiterate those arguments here.

First, the specification does not merely refer to WO 95/18856, as was true in *In re de Seversky*, cited in the Office Action. Indeed, WO 95/18856 is *expressly* incorporated by reference in the specification as filed. But the specification goes further yet. The specification states, specifically, that “[t]he invention further includes hedgehog compounds described in 95/18856 and here incorporated by reference, including homologs of hedgehog proteins, recombinant hedgehog proteins, ... [and] combinatorial mutants of hedgehog proteins as agonists or antagonists.... These and other compounds may be selected for modulating hematopoiesis and vascular growth according to the assays of the invention.” Although Applicants assert that this statement is sufficient to incorporate the *entirety* of WO 95/18856 into the specification, the present specification *also* points to a specific portion of the prior application, that portion related to the hedgehog compounds such as those recited thereafter, even though this portion is defined by subject matter rather than by line and column numbers.

Applicants respectfully direct the Examiner’s attention to *Telemac Cellular v. Topp Telecom*, 247 F.3d 1316, 1329, 58 U.S.P.Q.2d 1545 (Fed. Cir. 2001), which states, “[w]hen a document is ‘incorporated by reference’ into a host document, such as a patent,

the referenced document becomes effectively part of the host document as if it were explicitly contained therein. *Advanced Display Sys. v. Kent State*, 212 F.3d 1272, 1282, 54 USPQ2d 1673, 1679 (Fed. Cir. 2000).” Of particular note is that the entire document is considered to be incorporated – not merely a portion. By the Office Action’s logic, such an incorporation would be an impossibility, because an entire document could not be incorporated by reference if it were required that “specific portions” be pointed out. Neither of the above-cited cases is an aberration. “As the expression itself implies, the purpose of ‘incorporation by reference’ is to make one document become a part of another document by referring to the former in the latter in such a manner that it is apparent that the cited document is part of the referencing document as if it were fully set out therein.” *Application of Lund*, 376 F.2d 982, 989 (C.C.P.A. 1967).

The Office Action cites and quotes MPEP 608.01(p) as exemplifying PTO policy and requirements for incorporation by reference. Although the MPEP is a fine and helpful reference, it is not the law. In fact, the very section cited by the Examiner was discussed at length in *Application of Hawkins* 486 F.2d 569 (C.C.P.A. 1973). “After reviewing the cases on the subject and the practicalities of the situation, the court concluded that the practice did indeed have longstanding basis in the law, and that necessarily the Commissioner of Patents is vested with wide discretion to formulate rules and guidelines governing its use, thereby to prevent its abuse.... However, in the present case, we find that the addition to the disclosure of the textual material originally incorporated by reference cured any defects it might have originally had as filed, and that the application is in compliance with section 112 of the statute.” *Hawkins*, 486 F.2d at 573.

The Examiner has pointed to *In re Hawkins* as a case in which a portion of a prior filing was incorporated by reference without reciting specific column or page numbers. However, this decision shows only that the incorporation in that case was permissible, and in no way indicates that the present incorporation is impermissible. Applicants need not conform to the Examiner’s selection of a particularly narrow fact pattern to justify incorporation by reference. The Examiner has cited not a single case that has denied incorporation by reference when the phrase “incorporated by reference” occurs in the specification in connection with a published document.

It is well settled that “the standard of one reasonably skilled in the art should be used to determine whether the host document describes the material to be incorporated by reference with sufficient particularity.” *Advanced Display Systems*, 212 F.3d at 1283. Applicants respectfully submit, however, that they have been unable to identify *any precedent* in which an incorporation by reference was found unsuccessful due to insufficient particularity. Other cases, should the Examiner choose to review them, reach a similar result. *Rolls Royce v. United States*, 339 F.2d 654, 168 Ct.Cl. 367 (Fed. Cir. 1964); *Technograph Printed Circuits v. Bendix Aviation*, D.C., 218 F.Supp. 1, 31, aff’d 327 F.2d 497 (4 Cir., 1964); *B. F. Goodrich v. U.S. Rubber*, D.C., 147 F.Supp. 40, 58, [FN11] aff’d 244 F.2d 468 (4 Cir., 1957).

Indeed, courts of appeals feel strongly about this issue: “Filing cabinets abhor redundancy. Warehouses covet their space. The overcrowded conditions of offices in this city are in direct ratio to the space needed for storing of documents. The Patent Office was conceived by a document and has been prolific in that regard from its inception. These considerations warrant an economizing of words so as to alleviate these serious conditions. We do not feel that this economy will be at the expense of clarity and thereby frustrate the effectiveness of the statute.” *General Elec. Co. v. Brenner*, 407 F.2d 1258, 1263 (D.C. Cir. 1968).

In summary, Applicants submit that there is no legal basis for the Office Action’s assertion that only a portion of a public document can be incorporated by reference, and that any such portion must be explicitly pointed out. Furthermore, even if such a requirement were in fact applicable, the specification as filed is more than sufficient to permit one reasonably skilled in the art to identify the portions of WO 95/18856 that Applicants have incorporated into the present specification by amendment. This conclusion is underscored by the apparent lack of any legal precedents indicating that the words “incorporated by reference” are not themselves sufficient to effect the legal incorporation. Reconsideration and withdrawal are respectfully requested.

*Claim Rejections – 35 U.S.C. §112, First Paragraph*

Claims 57-73 and 82-144 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Applicants respectfully traverse this rejection to the extent it is maintained over the claims as amended.

First, Applicants respectfully point out that this rejection has been extended to the newly added claims – which differ substantially from the previously pending claims – without providing any legal reasoning why the new claims should be subject to the same rejection. What little is stated in the Office Action suggests that this rejection is tied to the alleged improper incorporation by reference discussed at length above. However, Applicants respectfully point out that the new claims do not employ the language or terminology incorporated by reference, and so should not be subject to this rejection for that reason.

Indeed, it is difficult to imagine the circumstances under which a means-plus-function claim could be rejected as lacking sufficient written description. As is clear from the very language of the statute, claims interpreted under 35 U.S.C. § 112, sixth paragraph, are construed to cover the corresponding structure, material, or acts described in the specification and equivalents thereof. Thus, the claims are so intimately tied to the disclosure of the specification – for the specification lays the foundation for the scope of the claim in an intimate and inextricable manner – that the claims by definition must be adequately described. If the Examiner bases this rejection on the equivalents that fall within the scope of the claim, Applicants direct the Examiner's attention to MPEP 2182: "The specification need not describe the equivalents of the structures, material, or acts corresponding to the means- (or step-) plus-function claims. See *In re Noll*, 545 F.2d 141, 149-50, 191 USPQ 721, 727 (CCPA 1976) ('The meaning of "equivalents" is well understood in patent law, ... and an applicant need not describe in the specification the full range of equivalents of his invention.' (citation omitted))." Applicants will address any additional issues surrounding the scope and interpretation of the recently added claims below.

With respect to the remaining claims, Applicants rely on the arguments provided above with respect to the propriety of the incorporation by reference to resolve this ground of rejection. Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

Claims 57, 58, 60-73, 82, 83, 85-96, 99-114, 117-132, and 132-144 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicants respectfully traverse this rejection to the extent it is maintained over the claims as amended.

As an initial matter, it is unclear why claim 58 is included in this rejection, when seemingly similar claims 84, 97, and 115 are excluded from this rejection. Clarification is respectfully requested.

Additionally, the rejection has been applied to the newly added claims without any reasoning that compares the scope of these claims with the enablement provided by the specification. Applicants respectfully request that the reasoning behind the rejection of these claims on enablement grounds be clarified on the record, both to assist Applicants in understanding and overcoming the rejection, as well as to develop the record for appeal.

As has been stated above, claims governed by 35 U.S.C. § 112, sixth paragraph, are construed to cover the corresponding structure, material, or acts described in the specification and equivalents thereof. The present claims use two different means-plus-function phrases: means for activating hedgehog signaling, and means for binding *patched*, and thereby activating hedgehog signaling. For both phrases, one of skill in the art would recognize that the corresponding materials in the specification are the naturally occurring hedgehog proteins and fragments thereof that bind to *patched*, and induce cells to undergo hematopoiesis – subject matter the Office Action concedes is enabled. For the

former phrase only, vectors, gene constructs, and other nucleic acids encoding such proteins or fragments would also qualify as means for activating hedgehog signalling. The equivalents within the literal scope of the claim, as has been pointed out above, are determined as a matter of law. Applicants invite the Examiner to make of record why Applicants are not enabled for use of a composition that is insubstantially different from a hedgehog protein, that is interchangeable with a hedgehog protein, or that performs substantially the same function, in substantially the same way, to achieve substantially the same result as the hedgehog protein itself.

Although Applicants have addressed the rejection relating to breadth of the compounds encompassed by the term "hedgehog compound" in the claims, Applicants reiterate those arguments here to prepare the record for appeal.

In evaluating the enablement of the claimed subject matter, both the courts and the MPEP have acknowledged that some experimentation is permissible, as long as that experimentation is not undue (MPEP 2164.04). "An extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance." *In re Colianni*, 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977). However, the courts have been clear that the determination of whether undue experimentation is required should not be made based solely on the time and cost involved in conducting such experimentation. "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed Cir. 1988). "Time and expense are merely factors in this consideration and are not the controlling factors." *United States v. Telectronics Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed Cir. 1988), *cert. denied*, 490 U.S. 1046 (1989).

The Examiner has stated that hedgehog compounds are too broadly defined to be enabled throughout their scope. Applicants respectfully direct the Examiner's attention to the portions of the claims correlating the structure of the hedgehog compounds to known hedgehog polypeptide sequences. Claims 57 and 83 recite a hedgehog compound that

comprises a polypeptide sequence at least 80% identical to a sequence selected from SEQ ID NO: 34, SEQ ID NO: 35, SEQ ID NO: 36, SEQ ID NO: 37, SEQ ID NO: 38, SEQ ID NO: 39, SEQ ID NO: 40, or a fragment thereof. Claims 88 and 95 recite a hedgehog compound that comprises a polypeptide sequence of SEQ ID NO: 41, SEQ ID NO: 42, or a fragment thereof. Claim 96 recites hedgehog compound comprises a polypeptide sequence encoded by a nucleic acid which hybridizes under stringent conditions, including a wash step of 0.2 x SSC at 65 °C, to a nucleic acid sequence designated in one of SEQ ID Nos. 27-33. In each case, the polypeptide sequence binds to *patched* and induces cells to undergo hematopoiesis. Applicants respectfully submit that any hedgehog compound that meets these structural and functional terms would be expected to be useful in the claimed methods.

The Examiner asserted that at the time the instant invention was filed, little was known about which parts of a hedgehog protein were responsible for activity, and asserted that across mammalian Shh proteins there is about 85% cross-species identity, while acknowledging that Shh, Ihh, and Dhh would be expected to function in the disclosed methods. Applicants again direct the Examiner's attention to Chang et al., already made of record, which indicates that Hhg-1, a mouse Sonic hedgehog gene, functions in *Drosophila* in a manner similar to the native *Drosophila* hedgehog protein, despite the fact that these polypeptides are only approximately 46% identical. Applicants have previously provided a copy of Dyer et al., *Development* **2001**, 128, 1717-1730, in which a number of experiments relating to hematopoiesis were performed in mice using human hedgehog proteins. Even if it is true that mammalian Sonic hedgehog proteins share only about 85% cross-species identity, the identity is lower among mammalian Sonic, Indian, and Desert hedgehog proteins taken together, and the functional interchangeability of *Drosophila*, mouse, and human hedgehog proteins suggests that one of skill in the art would expect many *non*-mammalian hedgehog polypeptides to functionally replace mammalian hedgehog polypeptides in the presently claimed methods. Furthermore, WO 95/18856, incorporated by reference into the present application, published well prior to the filing date of the present application, and included as reference AA in the first IDS filed in the present application, contains extensive

discussion of the portions of various hedgehog proteins that contribute to the biological activity of this family of signalling molecules. The art of record clearly indicates that significant variability can be tolerated, and thus one of skill in the art, guided by the level of knowledge in the art and the disclosure of the present application and references cited therein, would have no trouble practicing the presently claimed methods throughout their scope using only routine experimentation.

The only remaining question then becomes whether the making and testing of hedgehog compounds constitutes undue experimentation. WO 95/18856, referenced by and incorporated into the present application, discusses in great detail techniques for making and testing variant sequences. For example, WO 95/18856 discusses combinatorial mutagenesis at great length, and such techniques were highly developed in the art by the time the present application was filed. In addition, Applicants provide herewith as Exhibit A copies of Gallop et al., *J. Med. Chem.* **1994**, *37*, 1233-1251; Graham et al. *Biochemistry* **1993**, *32*, 6250-6258; Chan et al. *J. Bacteriol.* **1993**, *175*, 858-865; Osuna et al. *Gene* **1991**, *106*, 7-12; York et al., *J. Biol. Chem.* **1991**, *266*, 8495-8500; Sandberg et al. *Proc. Natl. Acad. Sci.* **1993**, *90*, 8367-8371; Wissmann et al. *Genetics* **1991**, *128*, 225-232; Delagrave et al., *Protein Engineering* **1993**, *6*, 327-331; and Reidhaar-Olson et al., *Science* **1988**, *241*, 53-57, all of which were published well in advance of the filing of the present application and support Applicants' contention that prior to the filing of the priority application, many articles had been published demonstrating the use of combinatorial mutagenesis to generate active variant sequences for a known sequence. Applicants point out in particular Reidhaar-Olson et al. and Delagrave et al. as describing especially powerful techniques for generating variant sequences.

Moreover, the present application provides an assay, described on pages 40-43, which can be employed for testing the activity of such variants for inducing hematopoiesis, in addition to the other assays described in WO 95/18856 and other literature references. High-throughput screening methods were in common use by the time the instant application was filed. Applicants additionally point out that claims 57-73 and 82-113 are explicitly limited to hedgehog compounds which possess specific



structural and functional characteristics. Accordingly, following the guidance provided in the specification and generally available in the art, one of skill in the art would be able to generate hedgehog compounds that meet the limitations of these claims without undue experimentation.

The Examiner has asserted that predictability is required. It is true that the scope of enablement depends in part on the predictability of the relevant art. However, it is not required that the invention be restricted in scope to absolute black-and-white predictability. The test of enablement is whether one of skill in the art could practice the invention throughout its scope without undue experimentation; predictability and foreseeability are relevant only to the extent that undue experimentation is necessary to practice the full scope of the pending claims. Technology available at the time of filing, as has already been made of record, permitted the preparation and testing of vast numbers of variant sequences with little or no human intervention whatsoever – the very essence of “routine experimentation.” The Office Action suggests that an “invitation to experiment” is not enough for patentability; however, if the invited experiments are merely routine, as here, no lack of enablement is present.

Lastly, Applicants respectfully point out that, despite the considerable weight apparently granted to the above factual assertions presented in the Office Actions, not a single reference has been cited in support of their veracity. If the Examiner is relying on a reference not of record, Applicants respectfully request that this reference be made of record in order that Applicants may more directly address its teachings. If the Examiner is relying on personal knowledge, Applicants respectfully request that the Examiner provide an affidavit pursuant to 37 C.F.R. 1.104(d)(2).

For the reasons set forth above, Applicants submit that the present claims are fully enabled throughout their scope.

***Claim Rejections – 35 U.S.C. §112, Second Paragraph***

Claims 57-73 and 82-144 are rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. Applicants respectfully traverse this rejection to the extent it is maintained over the claims as amended.

Claims 57, 83, 88, and 96 are rejected for reciting “functionally equivalent to a naturally occurring hedgehog protein”. Applicants have amended these claims to remove this limitation, thereby rendering this rejection moot. Applicants submit that the scope of these claims is not narrowed by these amendments.

Claims 114, 132, 137, and 144 are rejected because “the language does not appear in the specification”. Applicants respectfully point out that “structure disclosed in the specification is ‘corresponding’ structure only if the specification or prosecution history clearly links or associates that structure to the function recited in the claim.” *B. Braun Medical v. Abbott Laboratories*, 124 F.3d 1419 at 1424, 43 U.S.P.Q.2d 1896 (Fed. Cir. 1997). Thus, although Applicants submit that one of ordinary skill in the art would have recognized the corresponding structures in the specification from the description as filed, Applicants have made of record above which structures are asserted to correspond to this function in accordance with MPEP 2181. If the Examiner would prefer, Applicants will amend the specification to reflect this understanding as contemplated by the final paragraph of MPEP 2181. According to MPEP 2181, no more can be required of Applicants to comply with 35 U.S.C. § 112, second paragraph, and thus this rejection must be withdrawn. To the extent that any issue remains related solely to potentially duplicative claims, Applicants will consider cancelling such duplicative claims upon indication of allowability as to other issues; otherwise, Applicants wish all pending claims to be considered on appeal.

Claims reciting “human progenitor cells” are rejected as being unclear. Although Applicants submit that one of skill in the art would interpret this term as it is ordinarily used in the art and would not find the term ambiguous or otherwise be uncertain as to its scope. Nevertheless, Applicants have amended these claims to clarify the subject matter being claimed. Applicants submit that the scope of these claims is not narrowed by these amendments. Reconsideration and withdrawal of this rejection are respectfully requested.

### CONCLUSION

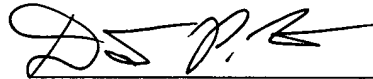
In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is

respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945.**

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Respectfully Submitted,



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